Antiretroviral Therapy Adherence Measurement and Support in South Africa: Initial Activities from July 4 to 26, 2005

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About RPM Plus

The Rational Pharmaceutical Management Plus (RPM Plus) Program, funded by the U.S. Agency for International Development (cooperative agreement HRN-A-00-00-00016-00), works in more than 20 developing countries to provide technical assistance to strengthen pharmaceutical and health commodity management systems. The program offers technical guidance and assists in strategy development and program implementation both in improving the availability of health commodities—pharmaceuticals, vaccines, supplies, and basic medical equipment—of assured quality for maternal and child health, HIV/AIDS, infectious diseases, and family planning and in promoting the appropriate use of health commodities in the public and private sectors.

Abstract

Global health is a critical target area for governments worldwide, as the pandemic of infectious diseases, and more specifically, HIV/AIDS undermines achievement towards international development goals. The U.S. Government, operating through the U.S. Agency for International Development and other organizations, has devoted significant attention and funds to the problem of HIV through the provision of substantial support to increase availability of HIV/AIDS treatment. While a cure for HIV remains elusive, antiretroviral therapy offers the best alternative. Highly active antiretroviral therapy effectively suppresses HIV in blood and tissues, restores immune function, and increases survival. To achieve these benefits, high levels of medication adherence are necessary. If adherence falters, resistance to antiretrovirals may develop, thus rendering the treatment regimen ineffective and possibly requiring a more costly and toxic regimen change.

The antimicrobial resistance (AMR) portfolio of RPM Plus is interested in the issue of adherence given the significant international efforts that have gone into ensuring the availability of antiretroviral therapy (ART). To promote rational use of antiretrovirals, the AMR portfolio included adherence to ART as a major activity for project year 5. This trip report describes the visit of Dr. Mohan Joshi and Ms. Sarah Paige to South Africa and captures more than just highlights of the visit, and includes information on the process of contextualizing the ART adherence activity in South Africa.

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Key Words and Terms

HIV/AIDS, antiretrovirals (ARVs), adherence, antiretroviral therapy (ART), ART adherence

Contents

Acronyms

AIDS	acquired immune deficiency syndrome
AMR	antimicrobial resistance
ART	antiretroviral therapy
ARV	antiretroviral
DHIS	Department of Health Information System
DoH	Department of Health
HAART	highly active antiretroviral therapy
HIV	human immunodeficiency virus
ICIUM	International Conference on Improving the Use of Medicines
MSH	Management Sciences for Health
NDoH	National Department of Health
PMTCT	preventing mother-to-child transmission
RPM Plus	Rational Pharmaceutical Management Plus program
USAID	US Agency for International Development
WHO	World Health Organization

Background

Global health is a critical target area for governments worldwide, as the pandemic of infectious diseases, and more specifically, HIV/AIDS undermines achievement towards international development goals. The U.S. Government, operating through the U.S. Agency for International Development (USAID) and other organizations, has devoted significant attention and funds to the problem of HIV through the provision of substantial support to increase availability of HIV/AIDS treatment.

While a cure for HIV remains elusive, antiretroviral therapy (ART) offers the best alternative. Highly active antiretroviral therapy (HAART) effectively suppresses HIV in blood and tissues, restores immune function, and increases survival.[1,2] To achieve these benefits, high levels of medication adherence are necessary.[3,4,5,6] If adherence falters, resistance to antiretrovirals (ARVs) may develop, thus rendering the treatment regimen ineffective and possibly requiring a more costly and potentially more toxic regimen change.[7,8,9] This problem in individuals poses a potential hazard to the community because ARV-resistant strains of HIV could then be transmitted. Although some recent literature presents a paradoxical relationship between resistance and medication adherence with regard to HIV[10], pooled data and lessons from other infectious diseases support the notion that adherence protects against resistance.

In 2003, the World Health Organization (WHO) convened a working group to review the literature around long term adherence within a chronic disease context. The WHO group defined long term adherence as "the extent to which a person's behaviour- taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider." [11] However, for the purposes of work on adherence by Rational Pharmaceutical Management Plus (RPM Plus) program, the intent is to focus specifically on *medication* adherence in both the short and long term.

Adherence to ART has been the subject of numerous research papers, conferences, and debates, yet an ideal adherence support model has not been identified. However, specific qualities of activities that are associated with high levels ART adherence have been agreed. Generally adherence support activities should be on-going, customized to the individual's need, culturally appropriate, and reflect a positive relationship between the patient and the health care provider. Examples of adherence support measures include education (both patient and provider), counseling for individuals infected and affected, financial incentives, directly observed treatment in classic or modified form, electronic reminders such as pagers or alarm clocks, peer support, pill boxes. Often adherence support efforts are comprised of a combination of activities.[12] Even as facilities acknowledge that adherence is a critical element of an ART program and implement adherence activities, the methods to measure adherence remain underdeveloped and frequently un-validated.

RPM Plus' Role in Promoting Adherence

The RPM Plus program provides technical leadership to global health initiatives though strengthening pharmaceutical management systems. The program supports USAID's global health priorities through its mandate to "improve the availability of quality pharmaceuticals, vaccines, supplies, and equipment and to promote the appropriate use of these health commodities in both the public and private sectors for USAID priority interventions." (www.msh.org/projects/rpmplus/2.1.htm) RPM Plus works on health systems infrastructure so that technical assistance may be designed from the onset for long term sustainability and aim to improve clinical outcomes across all disease areas.

With the current international spotlight on the HIV pandemic, RPM Plus is responding to the call for expertise to scale up AIDS treatment. Through partnerships with the Global Fund to Fight AIDS, Tuberculosis, and Malaria; the President's Emergency Plan for HIV and AIDS Relief; and the WHO's 3x5 plan, as well as with national and local governments, RPM Plus applies its proficiency in pharmaceutical management to the area of HIV/AIDS. For example, RPM Plus has developed information systems to facilitate the quantification, procurement, and tracking of ARVs, developed Standard Operating Procedures for labs and pharmacies within an HIV context, established a regional leadership forum of key health care providers and decision makers, and provides technical assistance towards developing and sustaining a healthy pharmaceutical management system that includes ARVs in partnership with governments of collaborating countries. (www.msh.org/projects/rpmplus/pdf/hiv_poster.pdf)

The Antimicrobial Resistance (AMR) portfolio of RPM Plus (www.msh.org/projects/rpmplus/3.4.htm) is appropriately positioned to address medication adherence. Adherence has long been considered a key element towards reducing the likelihood of the emergence and spread of drug resistant pathogens. Given the recent global efforts towards expanding access and availability of antiretroviral medicines, the case for adherence is even more relevant as HIV is highly mutable and requires lifelong treatment. Once the drugs are made available, to ensure favorable clinical outcomes patients must actually take the medicines as advised. It is this act of adhering to the medication regimen that comprises the final step in the RPM Plus goal of rational pharmaceutical management. Until now, RPM Plus' role in HIV/AIDS drug management has been on the side of scale-up of commodities; now that antiretroviral drugs are increasingly becoming more available, RPM Plus is developing activities to promote appropriate use of those drugs.

One specific example of RPM Plus' country level work in response to HIV/AIDS is in South Africa. There RPM Plus has been collaborating with the USAID mission and the Government of South Africa to strengthen pharmaceutical management systems to support scale-up of HIV/AIDS activities. Delivery, access and rational use of prevention of mother-to-child transmission (PMTCT) and antiretroviral therapy medicines and commodities are target areas of RPM Plus interventions.

The South African RPM Plus office is working collaboratively with South Africa's Department of Health at the National, and Provincial levels to implement the country's Operational Plan for Comprehensive HIV and AIDS Care, Management and Treatment. The RPM Plus interventions are tools to facilitate the government's ability to carry out the Operational Plan.

The AMR portfolio, in conjunction with RPM Plus/South Africa, has proposed an activity around adherence to ART that will further complement the South African government's efforts towards fulfilling its goal "to provide comprehensive care and treatment for people living with HIV and AIDS."[13]

Purpose of Trip

Dr. Mohan Joshi, RPM Plus Program Manager for AMR, and Ms. Sarah Paige, RPM Plus Program Associate for AMR, traveled to East London and Pretoria, South Africa, to initiate the ART adherence activity with the leadership of Gavin Steel, RPM Plus Senior Program Associate for South Africa and the RPM Plus/South Africa office. The main purpose of the trip was to explore the feasibility of launching the AMR portfolio's ART adherence measurement and support activity in South Africa.

Scope of Work

The scope of work for Mohan Joshi and Sarah Paige was:

1. Meet with Gavin Steel and J.P. Sallet to discuss the ART adherence activity
2. Draft plans to carry out the activity
3. Review and refine the draft data collection tools
4. Identify initial ART facilities for this activity
5. Meet with ART facility directors to assess interest/readiness for inclusion in pilot of data collection tools
6. Develop data management and analysis systems for hard copy and electronic information from participating facilities
7. Meet with other potential local partner groups and stakeholders relevant to ART adherence activities
8. Discuss logistics and coordination of further actions
9. Provide a debriefing to USAID, if requested

Activities

1. Meet with Gavin Steel to plan the ART adherence activity

Dr. Joshi arrived in East London and worked with Gavin Steel on July 5-8, 2005. During those meetings, they discussed in detail all aspects of the project proposal and extensively reworked the original proposal and roadmap drafted by the AMR portfolio on the proposed ART adherence activity. Ms. Paige joined on July 8. Dr. Joshi and Mr. Steel spent a number of days revising the two documents, and Ms. Paige merged the two in order to establish a single document to serve as a draft proposal that included an implementation plan. The proposal is now entitled "Improving Treatment Outcomes and Preventing Resistance to Antiretrovirals by Enhancing Adherence to Antiretroviral Therapy" and can be found in *Annex 1*. Work on the proposal continued into the beginning of the following week, after the team arrived in Pretoria. There, after a number of revisions, the draft proposal was deemed fit for presentation to the USAID mission and the National Department of Health.

The proposal presents, in detail, the purpose and plan to implement the AMR Adherence activity in South Africa. It contains a summary, background, general objectives, specific objectives, and then the steps towards implementing the activity. The proposal is contextualized for South Africa and includes elements that are specifically designed to support the national HIV/AIDS efforts.

Dr. Joshi, Mr. Steel and Ms. Paige traveled to Pretoria for the week of July 11th. Since Mr. J.P. Sallet, the Regional Technical Officer for RPM Plus/South Africa, was not available on July 11 and 12, Dr. Joshi, Mr. Steel and Ms. Paige met with him on the morning of July 13. He was briefed on the intent and progress of the activity. Dr. Joshi first described the background and overall intent of the activity, which is to design and implement a facility-based tool to monitor ART adherence, and to develop an "ART Adherence Update" newsletter to provide regular outreach to facilities on measures they can take to improve adherence. Mr. Steel outlined the steps planned in order to establish support for the activity by the National Department of Health (NDoH), as well as at the Provincial and local levels. Mr. Sallet's involvement in the process of gaining support by appropriate Department of Health (DoH) officials was expressly requested and thus, agreed. Relevant officials at various levels of the NDoH were identified.

Later, Mr. Steel discussed the ART Adherence monitoring tool and accompanying information system. Mr. Steel requested Mr. Sallet's input on identifying steps to prepare a discussion around linking the ART Adherence monitoring database to the Department of Health Information System (DHIS), and how to discuss adding a new indicator on ART adherence for inclusion in the DHIS in preparation for the upcoming meeting with the NDoH's Monitoring and Evaluation coordinator. The team anticipates that National Department of Health will be interested in the adherence monitoring information system and will request it be formatted or made available for inclusion into the DHIS. It was agreed that Mr. Steel and Mr. Sallet could develop some basic data analysis programming but that a local consultant would also possibly be contracted to further develop the data management system.

2. Review and refine the draft data collection tools

Early drafts of the adherence monitoring tool (developed by the AMR portfolio) were completely overhauled. The goal was to develop a simple, valid adherence monitoring form that would take only a few minutes to complete and was easy to use in both electronic and paper form. Since ART adherence monitoring already occurs at the facility, the tool is something ARV dispensing pharmacists will use during their regular counseling and dispensing sessions with clients. It is not intended to increase the already saturated workloads of health care providers at facilities. Informally, pharmacists regularly assess their client's ability to adhere and level of adherence, and then decide to whether to continue treatment. The tool aims to capture that conversation and translate it into useful data.

For the sake of this activity, ART adherence monitoring will be based on a combination of self report and pill count. The draft tool includes a set of self-report questions of a one week recall, and a component to reflect and calculate pill counts. Pill counts are currently the National HIV/AIDS Program's only mechanism to monitor and measure client adherence to ART. The new tool will include the pill counts as a way to capitalize on the objective monitoring measures already in place, and is introducing a second element of adherence monitoring, which is the self-report. The WHO's adherence working group indicated that no gold standard of medication adherence exists, but that self-report in addition to another objective measure can currently be considered the most valid tools.

The revised form was planned to be one page in length, and to include self report questions, pill count results, adherence counseling topics and counselors, and space on the reverse for further comment. Subsequent web searches were conducted on the various self report questions on medication adherence that have been used in different environments to further inform the tool's development. It was also suggested that the tool be further revised in conjunction with the ARV pharmacists at identified pre-pilot test sites so that the tool can be developed from the onset with insight of those who will be using it.

3. Identify pre-pilot ART facilities for this activity

Dr. Joshi and Mr. Steel visited the ART facility at Cecilia Makwane Hospital on July 7, 2005. There they met with Mark Patterson, the Chief Pharmacist, and Ntombi Ndandani, the ARV Pharmacist in Ward 5. Cecilia Makiwane hospital is a 680 bed hospital which serves as a level 2 referral institution with components of level 3 or tertiary care offered in designated departments. It was accredited as an ARV site during the first round of accreditation in July 2004 and currently serves 480 adult patients and 140 children. This center's referral base includes both peri-urban and rural patients. The team was exposed to the routine patient documentation and reporting associated with ARV treatment. Mr Patterson shared their experiences of an adherence measurement tool that was previously tried but subsequently discontinued. Both he and Ntombi reflected a keen interest in participating as a pilot site.

On July 8, 2005, Dr. Joshi, Mr. Steel, and Ms. Paige visited the ARV clinic at Frere Hospital to meet with the ARV pharmacist there, Andiswa Mngxe. The team discussed client-pharmacist interaction during ARV dispensing, both her formal and informal processes for determining adherence, and her willingness to utilize an ART adherence monitoring form. She indicated her

preference for an electronic form that requires a minimal amount of time to complete. The team also reviewed her electronic patient spreadsheets and reports and an example of a paper-based patient medical record, and visited the ARV and opportunistic infection pharmaceutical store room. The facility has been dispensing ARVs since June 2004 and currently serves over 400 HIV/AIDS clients.

Currently, the process for accessing ARVs at public facilities is comprised of a series of steps. Once individuals are identified as HIV positive, they are then referred to an ART facility for a clinical assessment to determine the client's physiological readiness to begin ART. Eligibility is determined by CD4 results as well as an evaluation of clinical symptoms. If the client is deemed eligible to start ARVs, an ART readiness program goes into effect. The readiness program includes a series of individual counseling sessions to educate the patient on HIV, the use of ARVs, appropriate nutrition, and social support networks. Once a patient has passed through this ART preparation program, his or her readiness to initiate ARTs is assessed and a physician makes the final decision as to whether treatment will begin.

Even with a thorough ART initiation process designed to ensure client adherence to ARVs and good clinical outcomes, long term medication adherence remains a challenge. Despite the Government's ongoing efforts to ensure access of ARVs by removing costs associated with treatment, significant barriers to adherence remain. Global experience finds that stigma, adverse reactions, complexity, drug resistance, opportunistic infections, weak social infrastructure, etc serve as challenges to any client's ability to maintain the regimen.[14]

4. Provide a debriefing to USAID

On the afternoon of July 12, Mr. Steel, Dr. Joshi, and Ms. Paige met with Ms. Anita Sampson, Health Project Manager at the USAID Mission in Pretoria and debriefed her on the ART adherence proposal using printed PowerPoint slides found in *Annex 2*. She was also given a copy of the detailed proposal (Annex 1). She asked if there was no tool already established for monitoring adherence and how the team planned on approaching the pharmacovigilance department at the National Department of Health. She also suggested that the team explore further as to the design of the adherence monitoring database to determine the level of synchronicity it ought to have with the DHIS. Ms. Sampson indicated that she would share the presentation and proposal with her colleagues involved in treatment as well as those mission staff working with the Presidential Emergency Plan for AIDS Relief.

5. Briefing to the South Africa RPM Plus Staff

In the afternoon of July 13, the RPM Plus/South Africa staff attended an informal PowerPoint presentation provided by Mr. Steel on the ART adherence activity. A meeting followed the presentation where the staff who were present provided feedback on the activity. Those in attendance included Mr. Steel, Dr. Joshi, Ms. Paige, Ms. Siziwe Qolohle, Ms. Valerie Tseladimitlwa, and Mr. Bada Pharasi. Issues that were raised included the need to translate the tools into the more widely spoken local languages, the possibility of piloting at three sites, the tool's application in a pediatric setting, and the application of the tool in generic chronic disease environments. The team took those points into consideration.

6. Further discussion on the RPM Plus Adherence Strategy

One additional component to the trip was further effort into the development of an RPM Plus adherence strategy. Mr. Steel, Dr. Joshi, and Ms. Paige spent some time on July 13th discussing an adherence strategy from the perspective of monitoring and improvement efforts. Ms. Paige spent the two days that she remained in South Africa working on a preliminary draft of that strategy, as well as conducting searches on medication adherence self report questionnaires.

7. Meet with National Department of Health

After the departures of Dr. Joshi and Ms. Paige, Mr. Steel and Mr. Sallet visited the NDoH on July 18, 2005. Their meeting was with the HIV directorate's treatment and support team. The ART Adherence proposal was submitted and the PowerPoint presentation of the proposed activity was given. A brief discussion followed to clarify various technical features of the presentation. The proposal was well received and Mr. Steel and Mr. Sallet were asked to present the proposal to the National Forum of HIV Directors on July 26, 2005. They were also asked to present the proposal with further technical information, so a revised presentation was completed by Dr. Steel and is attached as *Annex 3*.

8. Meet with Provincial Departments of Health

Mr. Steel met with the Eastern Cape HIV & AIDS Director , Dr. Namalanga Makwedini on the 21st of July 2005 . She was briefed regarding the progress made with regard to the proposed adherence project in order to canvas support at the national meeting on the 26th of July. The need for a coherent approach toward adherence issues was emphasized. Ms Makwedini indicated that there was a need to include adherence supporters in future training efforts.

9. Further meetings with key stakeholders in the NDoH

Mr. Sallet and Mr. Steel met with the HIV Task Group of the NDoH on July 26, which included all of the clusters associated with the HIV & AIDS Comprehensive Plan as well as provincial representatives. The team presented the proposal and included information on the tool as well as the adherence support activities. Response was favorable with comments to emphasize the following:

1. The tool must be scientifically sound yet simple
2. There should be a special effort to include pediatric issues
3. The need to pilot in each province was once again highlighted. The notion of a 1st pass in the Eastern Cape with two sites in each province thereafter was, however, adopted.
4. Regular feedback about progression and findings must be provided; Mr Steel undertook to do so, on a monthly basis.

Essentially Mr. Steel and Mr. Sallet secured approval at the provincial and national levels which subsequently allowed for the next phase of the activity, which is the technical implementation of the ART Adherence Monitoring tool.

Next Steps

Immediate Follow-up Activities

The immediate next steps include:

1. Coordination of pre-pilot with the two identified facilities
2. Revise the ART Adherence monitoring tool
    a. Utilizing a theoretical basis for drafting
    b. Further refinement will occur with ARV pharmacists in pre-pilot sites
3. Mr. Sallet and Mr. Steel will work further on developing the plan for an adherence database
4. Establish the framework for developing Standard Operating Procedures for use with the ART adherence monitoring tool
5. Meet with ART facility directors to plan for pre-pilot implementation.
6. Conduct the pre-pilot in two facilities in the Eastern Cape province

Subsequent Activities

The actual ART Adherence Monitoring and Support activity is more robust than has been described so far. Further implementation of the activity will reveal the various components involved. Some tasks will occur in concert. These have been distilled from the proposal.

1. Pre-Pilot Test- Conduct a pre-pilot test at two sites. Cecilia Makwane Hospital and Frere Hospital are under consideration. Piloting at two or more sites is desirable because of expected variations in facilities and patient characteristics.

2. Database and Data Management System- A database and data management system will be developed to manage ART adherence data. The data management and analysis system should provide each participating facility with stratified adherence rates on a quarterly and annual basis.

3. A National Consultative Meeting will be held to share the results of the pre-pilot test. As those findings are shared, the meeting will also serve as a strategizing effort to plan the nationwide implementation of the adherence measurement tool.

4. Nationwide adherence measurement tool pilot implementation- Implement widespread utilization of the adherence assessment tool and data management system. The initial set of facilities should include a reasonable representation of rural and urban sites across all provinces and metros.

5. ART Adherence Updates- Training on the adherence assessment tool will accompany the tool's implementation as it undergoes testing at provinces nationwide. One component of that training will be the initiation of the ART Adherence Updates. As updates are developed and completed, they will be disseminated to participating facilities.

The preceding activities will generate data on ART adherence rates amongst different facilities in a longitudinal manner and will place South Africa's NDoH in a position to identify relevant support required to strengthen adherence to ART. In this phase of the activity, strategies will be developed to support the implementation of relevant ART adherence improvement interventions.

As baseline data becomes available, and research on ART adherence interventions reveals promising interventions, a logical next step would be to support testing select adherence support interventions. Adherence data would continue to be collected as a way to monitor the effectiveness of the interventions. A call for medication adherence improvement interventions in partnership with universities and the medical research council would serve to stimulate research in the area of adherence and result in innovative approaches unique to and appropriate for resource constrained environments.

Technical assistance for this project will be provided to the National Department of Health by Rational Pharmaceutical Management Plus Program of Management Sciences for Health. Pilot testing and initial implementation of this NDoH project will be funded by US Agency for International Development. Successful demonstration of feasibility and usefulness of the activity will provide opportunity for the program to become sustainable by being integrated in the HIV/AIDS management program of the National Department of Health.

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Annex 1: Improving Treatment Outcomes and Preventing Resistance to Antiretrovirals by Enhancing Adherence to Antiretroviral Therapy

July 12, 2005

Draft Proposal

Summary

This proposal aims to establish mechanisms for measuring and supporting medication adherence over the long term. It is comprised of an antiretroviral (ARV) adherence measurement tool accompanied by identification and support of adherence improvement interventions. Patient medication adherence will be determined using self-report and pill count. The tool will be carefully designed so that adherence trends over time within and among facilities can be characterized. Individual level patient adherence data can be used by providers to address patients' adherence needs, while facility-level interventions may also be promoted by the National Department of Health to address adherence gaps within the system. Tool development will occur with significant input and guidance from key stakeholders and decision makers. As a complement to the adherence assessment tool, an "ART Adherence Update" newsletter will be disseminated to participating facilities on a regular basis, providing rich yet condensed information on adherence support measures, particularly suitable for resource constrained environments. Implementation of the activity will assist facilities to further align their ART programs with the national ART efforts. The use of the adherence measurement tool and inventory of adherence support interventions will allow for the establishment of baseline and follow up information on adherence, thus supporting the process of auditing and monitoring of the program's level of success over time. This critical endeavor will result in improved clinical outcomes as adherence is crucial for effective HIV/AIDS management, and will position South Africa as a lead country in Africa on adherence related issues for diseases requiring long term treatment.

Background

Highly active antiretroviral therapy (HAART) effectively suppresses human immunodeficiency virus (HIV) in blood and tissues, restores immune function, and increases survival.[1,2] To achieve these benefits, high levels of adherence to HAART is necessary.[3,4,5,6] If adherence falters resistance to antiretrovirals (ARVs) may develop, thus rendering the treatment regimen ineffective and possibly requiring a more costly and potentially more toxic regimen change.[7,8,9] This problem in individuals poses a potential hazard to the community, because ARV-resistant strains of HIV could then be transmitted. Although some recent literature presents a paradoxical relationship between resistance and adherence with regard to HIV, pooled data and lessons from other infectious diseases support the notion that adherence protects against resistance.

Global experts have yet to reach consensus on minimum levels of adherence allowing for optimal clinical outcomes. Early trials suggested that >90% adherence was required for virological suppressions.[10] These trials, however, involved only protease inhibitor (PI)

monotherapy. Two recent studies have substantiated the need for >95% adherence for non-boosted PI containing regimens. Research regarding the required levels of adherence on NNRTI-based regimens indicate lower levels of adherence (74 to 93%) are sufficient to maintain viral load suppression (< 400 copes/ml).[11] While these results reflect the minimum levels of adherence required to maintain viral load suppression, follow up on study participants was limited and did not address the potential for the development of drug resistance. Further investigation is needed to establish better evidence in this area.

Not only is there lack of consensus on optimal ART adherence levels, but variations in the definition of adherence exist between academic and clinic settings. Observational data indicate that a discrepancy exists with a strict definition of medication adherence. For example, in a clinical setting, medication "adherence" may be defined as a patient taking 74% of their medicines whereas in the literature, a patient is "adherent" when he or she is taking medicines correctly 74% of the time. A standardized definition of ART adherence is required to complement any adherence initiative.

High adherence levels have been difficult to maintain for patients receiving HAART in both industrialized and resource constrained settings. In many environments, one-fourth or more of patients are unable to maintain long term ART adherence >90%.[12,13,14,15] Various factors that may contribute to poor medication adherence include mental illness, regimen complexity, financial constraints, and medication side effects.[16]

Diverse interventions have been used in an effort to improve medication adherence. These can be grouped into the following four categories:

1. Patient education on HIV/AIDS and ART
2. Provider education on HIV/AIDS and ART
3. Psychological and social screening of patients to assess readiness for treatment
4. Provision of support services to facilitate resolution of barriers to adherence

Generally, these interventions are resource-intensive (human, financial, and infrastructural), not predictably effective, and of widely varying and unstipulated cost. Few studies have examined the impact of selected interventions and the findings remain ambiguous.[17,18] The effectiveness needed to justify the deployment of resources for selected interventions has been modeled for high resource settings,[19] but has not been established for resource constrained environments.

Assessing adherence to medication regimens in general and ART in particular is especially difficult because of the need for longitudinal data and the lack of validated medication adherence indicators.[20,21,22] For example, self-reporting overestimates adherence; electronic monitoring is costly, requires technology capabilities, and can underestimate adherence; pill count can be falsified and is impractical in busy clinic settings; and drug level assay is technically difficult, costly and requires a high level of expertise.[23,24] The WHO Consultation on adherence to long term therapies concluded that no single medication adherence measurement strategy is optimal. Instead, a multi-method approach that combines feasible self reporting and a reasonable objective measure is the current state of the art measurement. The current guidelines in South Africa rely solely upon pill counts which have been shown to overestimate adherence. As such, there is a need to develop a self reporting measurement tool to support pill count.

The importance of medication adherence is emphasized by international organizations,[25] and various manuals offer carefully considered approaches to its improvement. [26,27] The first edition of the South Africa Department of Health's National Antiretroviral Treatment Guidelines (Section 3) highlights medication adherence as an essential element to maintain the health benefits provided by ART. Clinicians are required to monitor and evaluate adherence, and respond appropriately. In support of this mandate the guideline indicates the need for training as a means to ensure patient adherence to ART. Currently, the guideline calls for a pill count and routine patient counseling to determine medication adherence. Chapter XI of the Operational Plan for Comprehensive HIV and AIDS Care, Management and Treatment for South Africa lists patient adherence as one of the functional elements of the patient information system. Despite the clear articulation of ART adherence measurement and support as an essential element of the program, details regarding the practice remain undefined. This project proposes a systematic approach that will address both the patient information systems and clinical monitoring and evaluation requirements of the plan.

The proposed activity is designed to help facilities that provide antiretroviral treatment measure and improve adherence of their patients to antiretroviral regimens, resulting in better clinical outcomes and preservation of effectiveness of ARVs.

The activity is unique in that it aims to establish a standardized, formal approach to the definition and measurement of ART adherence, and to address adherence over the long term as adherence rates drop off over time. Given the ART roll out is a relatively new initiative, the impact of delayed adverse drug reactions and improved health status on subsequent medication adherence rates is unknown. The activity will help track ART adherence rates over time that will allow repeated comparison of medication adherence rates and support measures within and among facilities.

Objectives

The primary objective of the project is to improve patient adherence to ARV regimens by providing ART facility staff with tools to collect, analyze, and use information, longitudinally, that will enable them to make well informed decisions about adherence support measures for their patients.

The secondary objective is to provide the National and Provincial Departments of Health access to information concerning medication adherence rates and adherence support measures at ART facilities so that they may take a leadership role in formulating evidence-based adherence approaches to improving ARV adherence. Potential outputs include a listing of interventions associated with high medication adherence, models of the outcomes of various ART adherence support strategies, and adherence support strategies practicable in resource constrained settings. Decision makers will be able to use the information in national health policy and planning. These efforts will also contribute to overall strengthening of health systems as medication adherence monitoring and support measures are generic tools that may be applied to settings providing treatment for other chronic diseases.

Specific Objectives

1. Establish a validated, standardized method of measuring ART adherence for the South African setting utilizing information obtainable from routine patient management that allows for standardized, longitudinal comparison of findings across facilities. This will be achieved by providing a tool that treatment facilities can use:
    - To record adherence rates of individual patients to specific ARV regimens
    - To periodically (e.g., quarterly) measure the impact of adherence support interventions and summarize ARV adherence of the facility's patient population. This information will feed directly into the database of information for use by the National Department of Health (NDoH) in policy development
    - To generate longitudinal medication adherence data

2. Coordinate comparisons of participating facilities' routine antiretroviral adherence practices in order to develop an organized and sustainable ART adherence approach for the long term.
    - Conduct a periodical inventory of ART adherence support practices in place at participating facilities
    - Utilize data collected from different environments to inform policy development regarding adherence monitoring and support measures.
    - Develop a continually updated database of information on adherence monitoring and adherence support measures obtained from participating facilities for use by the NDoH

3. Provide up-to-date information on effective medication adherence support measures
    - Regularly provide "ART Adherence Update" newsletter to facilities that include relevant findings concerning the effectiveness adherence interventions particularly suitable for resource constrained settings

4. Encourage networking and coalition building
    - Participating facilities and individuals support each other through a network that favors continuous discussion and sharing of experiences
    - Support research hypotheses and discussion on ART adherence support interventions
    - Improve ART facilities' capacity to interpret and respond to the adherence measurement information gathered

5. Support regional African ART adherence collaboration with South Africa as a lead country
    - A longer term objective is to develop a network of expertise and facilities so as to establish South Africa as a Regional Pharmaceutical Technical Collaboration (RPTC) center for adherence related matters. The summation of efforts will result in the establishment of South Africa as a regional leader in the field of adherence.

Components of the Proposed Approach

A start up *inventory of medication adherence support measures* being practiced at participating ART facilities will be performed and reviewed periodically. This inventory will allow for the

identification of those interventions and accompanying circumstances that hold the greatest impact upon adherence. It is envisaged that the collective influence of experience, the "ART Adherence Update" newsletter and other education interventions by the program will alter the profile of the inventory. Hence, one will be able to measure the effect of either adding or removing a given intervention. The use of the adherence measurement tool and support inventory will allow for the establishment of baseline and follow up information on adherence, thus supporting the process of auditing and monitoring of the program's level of success over time.

An *adherence measurement tool* will be developed from published evidence and validated for the South African environment. The tool will generate longitudinal observational data from a resource constrained environment.

- The basic foundation of the tool is an interview-based self report questionnaire and pill count in accordance with the WHO's (2003) "Adherence to Long Term Therapies" recommendations. The self report has not been widely used in South Africa but is a component of this activity as an additional adherence indicator to pill count. Variable ART adherence support measures, barriers to adherence, and a counseling report will also be included. The tool will be capturing routine practice data and does not call for additional measures or data generation. The instrument will be compatible with patient care practices and record systems at most ART facilities and will entail minimal burden to participating facilities.

- The tool will consist of unambiguous questions and will be accompanied by detailed instructions and training to minimize incorrect entry of information. A Standard Operating Procedure (SOP) and practice manual to accompany the tool will be developed and refined according to the principles of the quality improvement cycle.

- Training on adherence matters and use of the tool will accompany facility uptake. The training will consist of sharing adherence related experiences among facility personnel, a general adherence presentation, and specific training on the adherence measurement tool.

- The use of the medication adherence assessment for the self report component of the tool will contribute to the process of validation of adherence indicators. This will develop local health indicator validation skills, provide an evidence base for standardized adherence monitoring practice, and will measure the scalability of the tool and its feasibility in resource constrained settings.

- In order to identify facility level adherence measures that impact ART adherence a quarterly inventory of adherence support measures will be recorded. These may include provider, caregiver, or patient trainings, establishment of support groups, etc.

- The original tool will be piloted in two centers and the results presented to a national consultative forum involving key stakeholders and opinion leaders.

An individual and population based ART *adherence database and data management system* will be developed in association with a health information systems expert. It will be performed in either an electronic or paper format, and allows for determination of

  - Medication adherence rates

  - Successful intervention strategies (pill boxes, diaries, reminders, counseling, referral, etc)
  - Counseling techniques that resolve ART adherence barriers given a certain patient profile
  - Stratified ART adherence rates according to factors such as regimen, age, gender, level of knowledge, etc. The database will allow for cross-referencing with other national health databases

- Adherence results and adherence support information at each facility will be reviewed periodically (at least quarterly). Based on those results, facilities will be able to review their ART adherence support measures and modify appropriately.

- The data management system will be designed in such a way that it allows manual or electronic data entry, management, and interpretation so that the same system can be applied in settings lacking electronic facilities. This will be important as it is rolled out into severely resource constrained settings.

- It should also allow results to be entered into a computerized system at the facility, provincial or national level. Detailed instructions and worksheets for data entry should be provided. Specific characteristics of the instrument will be established in collaboration with the National Department of Health. Reports and interpretation will be disseminated to all relevant parties.

- The database will provide data to inform policy and planning as well as identify facilities requiring further medication adherence support and training

A complementary activity that will be developed in concert with the implementation of the adherence assessment tool is the "*ART Adherence Update*." The update is a newsletter designed to provide guidance to facility ART providers on adherence support measures and interventions. This will run in parallel with the implementation of the adherence tool and will describe innovative and effective interventions to support adherence initiatives relevant to resource constrained settings. The update will provide a summary of information about the design, content, required resources, and effectiveness of these interventions along with a critical interpretation of the information. The update will be deployed in a periodic fashion presenting new developments in the literature and practice insights as they are elucidated through the use of the adherence assessment tool.

- The ART Adherence Updates will largely focus on characterizing interventions examined in resource constrained settings. Interventions that appear relevant but examined in only high resource settings may also be included.

- Information will be disseminated and participants will be encouraged to archive updates and refer to them in the future. The updates themselves will provide small bits of information on a regular basis. They will target only a single intervention at a time and will be modeled on a newsletter format.

- The profile of updates will also be adapted to a power point format for use as an in-service training tool at the facility level

Sequence of Steps

1. ARV Adherence Measurement Tool- Develop an instrument to record medication adherence of individual patients at an ART facility.
    - A draft version has been developed and is under revision
    - Develop an accompanying SOP, practice manual, and training
    - Initiate the ART adherence support measures inventory

2. Pilot Test- Conduct pilot test at two sites. Cecilia Makwane Hospital and Frere Hospital are under consideration. Piloting at two or more sites is desirable because of expected variations in facilities and patient characteristics.
    - Meet with NDoH to present the proposal and refine appropriately
    - Review the proposal with the provincial health department and discuss proposed sites
    - Present pilot plan to the facility head
    - Convene a start-up meeting at pilot facilities
    - Conduct pilot test for one month
    - Collect and analyze findings and feedback
    - Present medication adherence tool and pilot data results to a National Consultative Meeting. During the meeting, the group will determine criteria to select facilities for small-scale nation wide implementation, inventory potential facilities, and establish a process for widespread implementation.
    - Revise tool, manual, and training according to facilities' feedback and input from National Consultative process

3. Database and Data Management System- A database and data management system will be developed to manage ART adherence data. The data management and analysis system should provide each participating facility with stratified adherence rates according to determining factors on a quarterly and annual basis.
    - Select a local expert to help design the data management and analysis system
    - Ensure that the ART adherence assessment tool format is suitable for both manual and electronic entry and analysis
    - Determine data collection procedures
    - Establish data elements and relationships
    - Develop software for data analysis allowing compilation of information on adherence and adherence support interventions at individual facilities and support interventions in relation to other participating facilities. Ensure that software facilitates data acquisition and flexible reporting
    - Identify potential data collection, management, and evaluation systems for review by the National Department of Health
    - Determine and document a system for the generation of reports and interpretations of data as well as dissemination to all relevant bodies

4. Nationwide adherence measurement tool implementation- Implement widespread utilization of the adherence assessment tool and data management system as determined by the National Consultative process. The initial set of facilities should include a reasonable representation of

rural and urban sites across all provinces and metros. In addition to public health sector facilities, it is recommended that the tool be piloted in faith based organization treatment facilities as well as the private sector. Level of willingness to participate in the program will be a key criterion for selection.

- Implement the tool by province, one facility per province is the aim for this initial nationwide implementation
- Continue to inventory adherence support measures and establish mechanisms for periodic review of interventions
- Utilize the revised tool, users' manual, and training program
- Establish baseline of adherence figures using self report and pill count

5. ART Adherence Updates- Training on the adherence assessment tool will accompany the tool's implementation as it undergoes testing at provinces nationwide. One component of that training will be the initiation of the ART Adherence Updates. As updates are developed and completed, they will be disseminated to participants.
    - Develop an archiving mechanism that includes a short background document on adherence, and briefs on types of adherence interventions
    - Review published and unpublished literature for information on adherence interventions
    - Work in collaboration with local graphic artists to format and set the ART Adherence Update style and presentation
    - Incorporate results of ART adherence support measures audit

Follow up

The preceding activities will generate data on ART adherence rates amongst different facilities in a longitudinal manner and will place South Africa in a position to identify relevant support required to strengthen adherence to ART. In this phase of the activity, strategies will be developed to support the implementation of relevant ART adherence improvement interventions.

As baseline data becomes available, and research on ART adherence interventions reveals promising interventions, a logical next step would be to support testing select adherence support interventions. Adherence data would continue to be collected as a way to monitor the effectiveness of the interventions. A call for medication adherence improvement interventions in partnership with universities and the medical research council would serve to stimulate research in the area of adherence and result in innovative approaches, unique to resource constrained environments. A dissemination, publication, and presentation strategy will be developed with all parties concerned.

Technical assistance for this project will be provided to the National Department of Health by Rational Pharmaceutical Management Plus Program of Management Sciences for Health. Pilot testing and initial implementation of this NDoH project will be funded by US Agency for International Development. Successful demonstration of feasibility and usefulness of the activity will provide opportunity for the program to become sustainable by being integrated in the HIV/AIDS management program of the National Department of Health.

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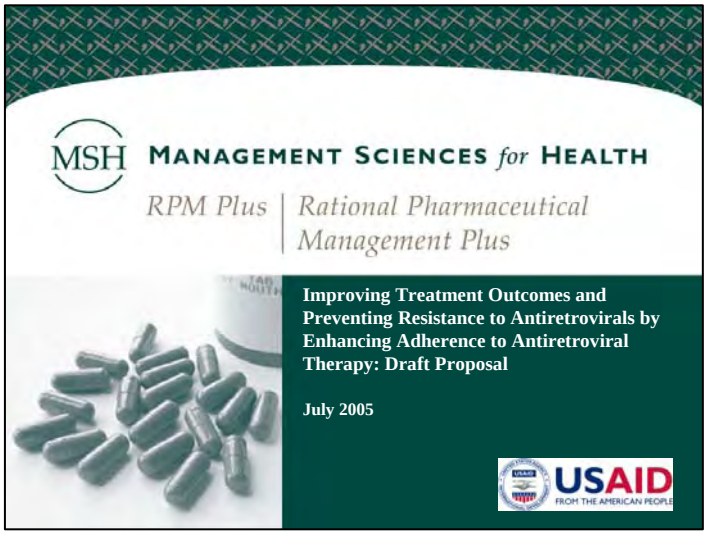
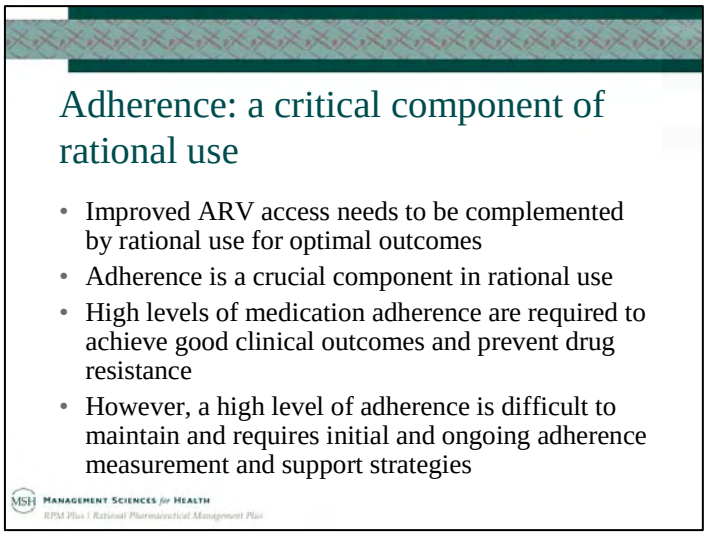
Annex 2: Powerpoint Slides Presented at USAID Mission in South Africa on July 12, 2005





The Proposed ART Adherence Activity in South Africa……

……is expected to help achieve better clinical outcomes and preserve the effectiveness of ARVs by preventing resistance

MSH Management Sciences for Health
RPM Plus | Rational Pharmaceutical Management Plus

Overall Objective of the Activity

is to help ART facilities in South Africa to measure and improve adherence of their patients to ART and to establish South Africa as a facilitator for Regional Technical Collaboration on ART adherence

MSH Management Sciences for Health
RPM Plus | Rational Pharmaceutical Management Plus

Specific Objectives of the Activity

- Establish a standardized method of measuring ART adherence
- Generate longitudinal ARV adherence data and enable intra- and inter-facility comparison of adherence rates and practices to identify effective adherence support measures
- Provide up-to-date information on effective adherence support measures to participating facilities

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Specific Objectives of the Activity (2)

- Provide the National Department of Health information concerning ART adherence rates and support measures in order to formulate evidence-based adherence improvement approaches for use with the National HIV & AIDS Program
- Encourage networking and coalition building around adherence issues among participating ART facilities
- Develop expertise so as to establish South Africa as a facilitator for Regional Technical Collaboration on ART adherence

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Steps to Implement the Activity

- Develop adherence measurement tool and users' manual
- Develop a database and data management system
- Pilot Test the draft tool at 2 ART sites (Eastern Cape - Cecilia Makwane Hospital and Frere Hospital)
- Present findings at a National Consultative Meeting and seek suggestions
- Implement the activity nation-wide on a small-scale (including adherence measurement tool and inventory of support interventions)

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Steps to Implement the Activity (2)

- Provide regular "ART Adherence Update" (newsletter describing adherence support options suitable for resource-constrained environments)
- Identify and implement appropriate training and other strategies to promote adherence
- Monitor adherence rates within and between facilities periodically to assess changes overtime

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Immediate Next Steps

- Present the proposal to USAID Mission and seek feedback and comments
- Present the revised proposal to the National Department of Health (NDoH) and seek approval
- Present to provincial Department of Health
- Revise the draft adherence measurement tool
- Present the plan for pilot testing to the two ART facilities and carry out the pilot test

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Support for the Proposed ART Adherence Activity

- Technical assistance to NDoH will be provided by RPM Plus/MSH. Pilot testing and initial implementation of this NDoH project will be funded by USAID.
- Successful demonstration of feasibility and usefulness of the activity will provide opportunity for the program to become sustainable by being integrated in the HIV & AIDS management program of NDoH

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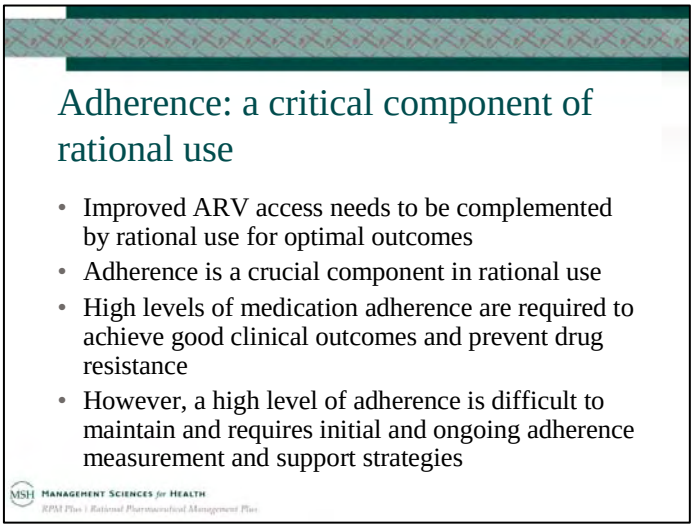
Annex 3: Powerpoint Slides Presented at the National HIV Directorates Meeting held on July 26, 2005



The Proposed ART Adherence Activity in South Africa……

……is expected to help achieve better clinical outcomes and preserve the effectiveness of ARVs by preventing resistance

MSH Management Sciences for Health
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Specific Objectives of the Activity

- Establish a standardized method of measuring ART adherence
- Generate longitudinal ARV adherence data
  - ~ enable intra- and inter-facility comparison
  - ~ identify effective adherence support measures
- Provide up-to-date information on effective adherence support measures to participating facilities

MSH Management Sciences for Health
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Specific Objectives of the Activity (2)

- Encourage networking and collaboration around adherence issues among participating ART facilities
- Develop expertise so as to establish South Africa as a facilitator for Regional Technical Collaboration on ART adherence

MSH Management Sciences for Health
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Overall Objective of the Activity

- To help ART facilities in South Africa to measure and improve adherence of their patients to ART and share lessons learned

MSH Management Sciences for Health
RPM Plus | Rational Pharmaceutical Management Plus

Steps to Implement the Activity

- Develop adherence measurement tool and users' manual
- Develop a database and data management system
- Pilot Test the draft tool at 2 ART sites (Eastern Cape - Cecilia Makwane Hospital and Frere Hospital)
- Present findings at a National Consultative Meeting and seek suggestions
- Implement the activity on a national scale (including adherence measurement tool and inventory of support interventions)

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Steps to Implement the Activity (2)

- Provide regular "ART Adherence Update" (newsletter describing adherence support options suitable for resource-constrained environments)
- Identify and implement appropriate training and other strategies to promote adherence
- Monitor adherence rates within and between facilities periodically to assess changes overtime

MSH Management Sciences for Health
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Immediate Next Steps

- Present the proposal to USAID Mission and seek feedback and comments
- Present the revised proposal to the National Department of Health (NDoH) and seek approval
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Support for the ART Adherence Activity

- Technical assistance (piloting and consultation) will be provided by RPM Plus/MSH
- Successful demonstration of feasibility and usefulness of the activity will provide opportunity for the program to become sustainable by being integrated in the HIV and AIDS management program of NDoH

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Predictors of Adherence

Reiter and by Ickovics et al

1. Socio demographic factors
2. Treatment Regimen
   - Pill Burden
   - Complexity
3. Disease Characteristics
4. Patient-Provider Relationship
5. Clinical Setting

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Effective self-management of chronic illness

- Patient Context
  - Socio-cultural context
  - Patient context
  - Coping with illness and regimen
- Health Provider Context
  - Health systems context
  - Staff attitude
  - Type of service

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Interventions to Promote Adherence

- Patient Education and Collaborative Planning
- Adherence Case Management
- Directly Observed Therapy
- Self-management education
- Simplified Treatment Regimens
- Adherence Devices
- Medication Organizers & Reminder Devices
- Visual Medication Schedules

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Validation - Electronic Bottle Caps

- Caps harbor chips that register each time a bottle is opened or closed
- Medication Event Monitoring System - MEMS

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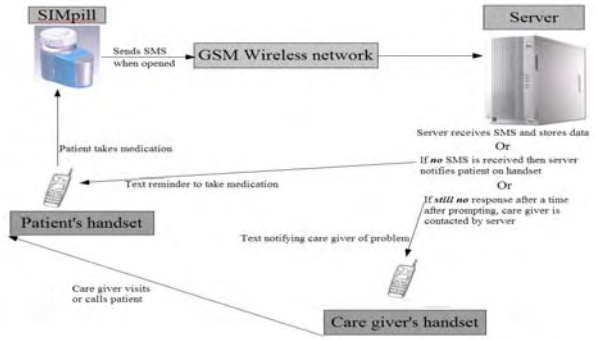
Validation - SIMpill



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Self-Reported Adherence Assessment Tool

- Questions with probes
- Trials - ACTG Adherence Baseline Questionnaire
  - 9 pages of questions
  - Takes 10 min
- Duong et al
- Morisky et al 1986
  - Validated in HIV – GEEMA Study 2002
  - 4 to 9 basic questions that are scored

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Morisky Questions

- Do you ever forget to take your medicine?
- Are you careless at times about taking your medicine?
- When you feel better do you sometimes stop taking your medicine?
- Sometimes if you feel worse when you take the medicine, do you stop taking your medicines ?

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GEEMA Morisky modification

- Thinking about the last week. How often have you not taken your medicine ?
- Did you not take any of your medicine over the past weekend ?
- Over the past 3 months, how many days have you not taken medicine at all ? { *recall too long* }

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Development - Self-Reported Adherence Assessment

- Review literature
- Select questions
- Combine with “show & tell”
- Psychometrics review
- Piloting
  - MEMS
  - Practical facets
- Review

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Annex 4: Request for Country Clearance

Request for Country Clearance

TO: Anita Sampson, USAID/South Africa
Fatima dos Santos USAID/South Africa

FROM: Management Sciences for Health (MSH)/Rational Pharmaceutical Management Plus (RPM Plus) Program, Cooperative Agreement # HRN-A-00-00-00016-00

SUBJECT: Request for Country Clearance for travel to South Africa for Mohan Joshi and Sarah Paige from July 4th – July 17th, 2005

COPY: Anthony Boni/Global HPSR/CTO RPM Plus
Kama Garrison/Global HPSR
Douglas Keene, Director, MSH/RPM Plus
Maria Miralles, Deputy Director, MSH/RPM Plus
Michael Gabra, Program Manager for Africa, MSH/RPM Plus
J.P. Sallet, MSH/RPM Plus Regional Technical Advisor, South Africa
Mohan Joshi, Program Manager for AMR, MSH/RPM Plus
Sarah Paige, Program Associate for AMR, MSH/RPM Plus

1. The RPM Plus Program wishes to request country clearance for the proposed travel of Dr. Mohan Joshi, Program Manager for AMR for the period July 4 to 13, 2005 and Ms. Sarah Paige, Program Associate for AMR for the period July 7 to 17, 2005.

2. Background:

Management Sciences for Health (MSH)/Rational Pharmaceutical Management Plus (RPM Plus) Program has received funds from the USAID Mission in South Africa under the President's Emergency Plan for AIDS Relief to assist the Mission in supporting the national scale up of antiretroviral therapy (ART) activities and to meet health commodity needs in support of the expansion of HIV/AIDS programs. Highly active antiretroviral therapy (HAART) effectively suppresses HIV in blood and tissues, restores immune function, and increases survival. To achieve these benefits, near-perfect adherence to HAART is necessary. If adherence falters, resistance to ARVs may develop, undermining the effectiveness of ART. This problem in individuals also poses a serious hazard to the community, because ARV-resistant strains of HIV then can be transmitted to others.

Near-perfect adherence has been difficult to achieve for patients receiving HAART both in industrialized and in developing countries. In almost all settings, one-fourth or more of patients are unable to maintain adherence >90%. The recently held International Conference on Improving Use of Medicines (ICIUM 2004) recommended that countries implement systems to

ensure adherence as an integral component of antiretroviral therapy programs. Methods to assess adherence have not been standardized, and the interpretation of results can be difficult. Overall, there is a substantial need for validated, facility-based materials to characterize and interpret adherence to various ART regimens. Accordingly, the SO5/AMR Portfolio of RPM Plus/MSH is implementing an activity to develop operational tools to facilitate facility-based data collection to measure and interpret adherence, and to present options to improve adherence. RPM Plus proposes to initiate this antiretroviral adherence-related activity in South Africa to complement the overall ART program.

3. Purpose of proposed visit:

Dr. Joshi and Ms. Paige will travel to Pretoria and East London, South Africa, to initiate the ART adherence activity in South Africa, with the leadership of Mr. Gavin Steel and the RPM Plus/South Africa office.

4. Scope of Work for this visit is as follows:

The scope of work for Mohan Joshi and Sarah Paige during the proposed visit will include the following:

- Meet with Mr. Steel and Mr. J.P. Sallet to discuss the ART adherence activity
- Draft plans to carry out the activity
- Review and refine the draft data collection tools developed to measure and interpret ART adherence
- Identify potential ART facilities and make initial exploration for their interest/readiness to participate in the activity
- Discuss the approach to and logistics of data management and analysis systems for hard copy and electronic information from participating facilities
- Meet with other potential local partner groups and stakeholders relevant to ART adherence activities
- Plan immediate next steps in the process
- Provide a debriefing to USAID Mission, if requested

5. Anticipated Contacts:
   - Ms. Anita Sampson, USAID/South Africa
   - Mr. Jean-Pierre Sallet, MSH/RPM Plus Regional Technical Advisor
   - Mr. Gavin Steel, MSH/RPM Plus Senior Program Associate

6. Logistics:
   Dr. Joshi will arrive in Johannesburg on July 4, 2005. He will depart Johannesburg on July 13, 2005. Ms. Paige will arrive in Johannesburg on July 7, and depart July 17, 2005. The hotel for Dr. Joshi and Ms. Paige in South Africa is the Protea in East London and the Holiday Inn in Pretoria.

   No further Mission assistance is required.

7. Funding: The visit is supported by MSH/RPM Plus S05/AMR core funding.

Action: Please inform the RPM Plus Program whether country clearance is granted for the activity to take place as proposed. Please reply via e-mail to the attention of Anthony Boni, USAID/G/PHN/HN/HPSR, e-mail address: aboni@usaid.gov, tel (202) 712-4789, fax (202) 216-3702, and to Ms. Kama Garrison at kgarrison@usaid.gov. Please send carbon copies to Douglas Keene at dkeene@msh.org, Maria Miralles at mmiralles@msh.org, Mohan Joshi at mjoshi@msh.org, Sarah Paige at spaige@msh.org, and Lindsay Gibbs at lgibbs@msh.org.

Thank you for Mission cooperation.